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Consensus statements

Advanced epithelial ovarian cancer: 1993 consensus statements

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Summary

Background: Over the last few days of a 5-day international workshop held in June 1993, a group of specialists in the field of advanced epithelial ovarian cancer tried to reach consensus on a number of issues with implications for standard practice and for research.

Methods: Five groups of experts considered several issues which included: biologic factors, prognostic factors, surgery, management recommendations, dose intensity, supportive care, drug resistance, second-line treatment, investigational drugs, and tumour markers. Discussing the management recommendations, the group attempted to arrive at answers to four questions: Is there in fact a cure rate for advanced ovarian carcinoma? Are there prognostic factors which help to identify patients who will not do well with current therapy? What is the current best therapy for advanced ovarian carcinoma? What directions should research take in advanced ovarian cancer? In a plenary meeting these issues were discussed.

Results: Consensus statements were achieved on all topics mentioned above. This article reports on the statements written by the chairmen and approved by the consensus group.

Key words: consensus, ovarian cancer, prognostic factors, surgery, management, second-line treatment, new drugs, tumour markers

Biologic factors

The following consensus statements were obtained with respect to biologic factors in advanced epithelial ovarian cancer.

Clinical recommendations

Histopathologic analysis with DNA ploidy by flow cytometry, image cytometry, and morphometric analysis should be performed, on selected patients with ovarian cancer, especially those who have borderline, low grade, and/or early stage tumours. There should be an effort made to increase the availability of these tests and the training of pathologists in the techniques.

When these biologic assays suggest a good prognosis, that is in borderline tumours and well differentiated, well staged early tumours (IA IB, and IC), chemotherapy can be omitted.

Research recommendations

Histopathologic analysis with DNA ploidy by flow cytometry, image cytometry, and morphometric analysis should be applied and studied in prospective clinical trials. A particular emphasis should be on the determination of subsets of patients who may have chemotherapy omitted or modified as part of their treatment. The aim should be to find an index that predicts poor prognosis that might be applied to clinical management. Such an index would need to have more than 90% positive predictive value. Other biologic assays including HER-2/neu oncogene, ras, c-myc, p53, and EGF-R should be confined to the research setting and not be applied routinely in the clinical management of patients.

Surgery

Implications for standard practice

The following consensus statements were arrived at with respect to the role of surgery in advanced ovarian cancer.

Meticulous surgical staging for apparently early stage ovarian cancer is very important. This should include:

- peritoneal washings
- all peritoneal surfaces, including the diaphragm should be palpated
- bilateral salpingo-oophorectomy and total abdominal hysterectomy, although a unilateral sal-

pingo-oophorectomy without hysterectomy may be considered for those patients who wish to maintain fertility
- suspicious nodules should be biopsied
- infracolic omentectomy
- multiple peritoneal biopsies, including paracolic gutters, Pouch of Douglas and diaphragm
- ipsilateral pelvic lymphadenectomy

Repeat surgery for staging in indicated in patients who have been inadequately staged and in whom this will provide further information which will impact on treatment decision making.

Definitive conclusions regarding the role of surgery in advanced ovarian cancer is made difficult by the lack of randomized studies in this area. Nevertheless, radical surgical cytoreduction has been historically regarded as standard primary treatment for this group of patients. It was agreed that surgical resectability and ultimate prognosis are influenced by tumour biology and technical expertise. When performed by surgeons, who are knowledgeable about the disease and techniques for cytoreduction, optimal dissection to <1 cm residual nodules can be achieved in at least 70% of patients. Ideally, all macroscopic disease should be removed. Acceptable morbidity has been reported after these procedures in all studies. Discretion and experience are required in determining the radicality of tumour resection to avoid predictable impairment of quality of life. This kind of radical surgery requires an experienced team of surgeons, anaesthetists and other health care professionals used to dealing with this disease.

In patients with suboptimal primary surgery (for instance without attempted debulking at the initial laparotomy), intervention debulking surgery should be considered for patients with a response or stable disease. A trial confirming the benefit of intervention surgery is needed.

Outside a clinical research protocol, routine second-look laparotomy (defined as an exploratory laparotomy to assess the cancer status of a patient who has completed a programme of chemotherapy and is clinically free of cancer) cannot be endorsed.

Research initiatives

The role of secondary surgical cytoreduction at the time of relapse is unknown and criteria, especially for patients who relapse more than 12 months following original surgery remains to be defined.

Management recommendations

After the presentation of the data cited in Thigpen et al. [1], the group attempted to arrive at answers to four questions: Is there in fact a cure rate for advanced ovarian carcinoma? Are there prognostic factors which help to identify patients who will not do well with current therapy? What is the current best therapy for advanced ovarian carcinoma? What directions should research in advanced ovarian cancer take?

Rates of long-term survival

As supported by long-term follow-up data from the eleven trials reviewed, there are patients who survive for 10 years of more. For patients with large-volume disease, defined as those with stage IV disease or those stage III patients with nodules larger than two centrimetres remaining after initial surgery, the 5 year survival rate with platinum-based combination chemotherapy is between 10% and 20%. For patients with small-volume disease, defined as stage III patients with no nodules larger than two centrimetres in diameter remaining after surgery, the 5 year survival rate with platinum-based combination chemotherapy exceeds 20%. Whether these long-term survivors are in fact cured is debatable because there seems to be a continuing risk of relapse in the longest series.

Prognostic factors

Prognostic factors identified as significant in multivariate analyses in one or more of the trials reviewed include: age, performance status, cell type, grade, stage, volume and number of residual lesions in stage III patients, and the presence or absence of ascites. Older age, poor performance status, mucinous or clear cell histology, high-grade or stage IV disease, large-volume stage III disease, or the presence of ascites all predict for a poorer outcome in terms of progression-free interval and survival. In regard to volume and number of residual lesions, it was noted that definitions vary among the studies reviewed with no good basis for the selection of one single-cut-off point as the most appropriate. The only uniform agreement among the discussants recognized, was the most significant difference as occurring between those patients with any macroscopic disease as compared to those with microscopic or no residual disease.

Optimal chemotherapy

There was no uniform agreement on what constitutes the 'best' chemotherapy. There was agreement that active agents include at least the platinum compounds, alkylating agents, anthracyclines, and taxanes. Agents with probable activity include hexamethylmelamine, 5-fluorouracil, methotrexate and VP-16. Views on how best to utilize these agents differed among the group.

Certain features of an optimal regimen were defined. The single most important feature of appropriate chemotherapy is the inclusion of a platinum compound. Platinum-based chemotherapy yields superior response rates and progression-free survival and probably produces superior long-term survival as well, although this is not totally clear as yet.

A second important feature of appropriate chemo-

therapy is the use of combinations of agents. The weight of evidence favours superiority of platinum-based combination chemotherapy over single platinum compounds in regard to response rates, progression-free interval, and overall survival. Studies comparing three-drug combinations of a platinum compound, alkylating agent plus an anthracycline show no statistically significant advantage to two-drug combinations without an anthracycline. These trials do, however, uniformly have a small, non-significant difference favouring the anthracycline-containing regimen. To determine whether this small difference might in fact be significant, the Ovarian Cancer Meta-Analysis Project analyzed pooled data from four trials comparing cisplatin plus cyclophosphamide with or without doxorubicin [2]. The meta-analysis showed a statistically significant advantage for CAP over CP in frequency of pathologic complete responses (30% versus 23%) and in overall survival. Whether the observed differences are in fact related to differences in dose intensity between the CAP and CP regimens or to the presence of doxorubicin in the combination is unclear. The consensus was that either cyclophosphamide 750 mg/m^2 plus cisplatin 75 mg/m^2 every three weeks or cyclophosphamide 500 mg/m^2 plus doxorubicin 50 mg/m^2 plus cisplatin 50 mg/m^2 every three weeks represented acceptable standard therapy.

The choice of the platinum compound is subject of debate [3]. Carboplatin-based therapy was considered to be an acceptable choice in patients with suboptimal stage III and stage IV ovarian cancer. The regimen recommended is carboplatin 300 mg/m^2 plus cyclophosphamide 600 mg/m^2 every four weeks. The group recognized the growing enthusiasm for dosing of carboplatin according to calculation of a desired area under the plasma concentration by time curve (AUC) [4], but all clinical data comparing carboplatin-based therapy to cisplatin-based therapy to date use dosing according to body surface area. This is the basis for the recommendation of a regimen dosed according to more traditional methods.

Another major issue addressed in the discussion of 'best' chemotherapy was the number of cycles of therapy to be given. It was noted that most studies employed five to ten cycles of treatment. No well-designed randomized trial provides definitive answer as to how many cycles yield optimal results. There was general agreement that most responses occur within four cycles of therapy. The consensus recommendation was that at least six cycles of treatment should be given and that no concrete evidence shows that additional treatment produces benefit.

The final issue addressed in the discussion of 'best chemotherapy was the role of the taxanes. Consensus was obtained with regard to several observations. Paclitaxel (taxol) and docetaxel (taxotere) are definitely active in ovarian carcinoma. Paclitaxel at least produces responses in patients who are clinically resistant to the platinum compounds, an observation which suggests that these agents are non-cross-resistant with other active drugs. The one randomized trial comparing cisplatin plus cyclophosphamide to cisplatin plus paclitaxel shows the paclitaxel combination to yield statistically significant improvement in clinical response rate [5] and progression-free survival with survival yet to be analyzed. It was generally agreed that these data strongly suggest that paclitaxel 135 mg/m^2 over 24 hours followed by cisplatin 75 mg/m^2 every three weeks will be at least as good as cyclophosphamide and cisplatin. Opinion was divided as to whether this paclitaxel regimen could be stated to be superior in the absence of a confirmatory trial.

Research directions

Recommendations as to the choice of future research directions fall into four categories: prognostic factors, clinical trials, institutional capabilities, and quality control.

With regard to prognostic factors, the group recognized a need to standardize prognostic factors which have been demonstrated to be independent variables in published multi-variate analyses. Populations from which prognostic variables are obtained should be defined and standardized for comparative purposes. At present there are inconsistencies and a lack of agreement regarding some variables which should be measured.

Attempts to define the level of risk for patients with advanced ovarian cancer will best be achieved by the development of a prognostic index rather than by applying individual variables to each patient. In order to produce a prognostic index, a large data base including all reported independent prognostic variables should be created. This would include: FIGO stage, age, histologic type, tumour ploidy, morphometry, histologic grade, performance status, chemotherapy (platinum v no platinum, dose intensity for platinum), extent of initial disease (size of largest metastasis, number of metastatic nodules, presence or absence of ascites), post-surgical cytoreduction (size of largest remaing nodule, number of nodules remaining), and primary treatment location (cancer centre v community).

The general thrust of research should be to identify and to devise ways to use prognostic factors in the choice of appropriate therapy. Along this line, investigations should be undertaken to identify patient subsets which can be expected to fare poorly with current therapy. For such patients, innovative approaches should be explored. Efforts should also be directed to evaluation of certain new factors such as ploidy and their role in identifying poor prognosis subsets. Finally, analyses of existing databases should seek to define better small-volume and large-volume patient populations.

In the area of therapeutic clinical trials, a number of specific issues deserve to be addressed. First and foremost, the role of paclitaxel in first-line therapy should

be explored and confirmed. The GOG has a number of ongoing trials which look at dose/response relationships for paclitaxel in the salvage setting and at the relative role of paclitaxel and paclitaxel-containing combinations versus non-paclitaxel-containing combinations in the front-line setting. These studies, hopefully to be confirmed by other groups, should determine whether paclitaxel is in fact a valid part of front-line therapy for all patients with advanced disease and whether more toxic, high-dose schedules are in fact necessary.

The second major area worthy of attention in the clinical trial arena is the value of dose-intense approaches. Current evidence is at best confusing. Questions in this area which need to be addressed include the following: Is there a point beyond which further dose escalation yields only increased toxicity rather than enhanced benefit? Is dose-intensity the critical variable, or is total dose equally or perhaps more important? Should doses of at least certain agents be based on calculations to reach a certain AUC? Are very high dose approaches necessitating autologous bone marrow support or perhaps other protective measures of value?

There are other treatment related issues which should be considered for study in randomized trials. What is the role, if any, of doxorubicin in front-line therapy? What is the role of hexamethylmelamine in front-line treatment? Should choice of chemotherapy for small-volume disease be different from that for large-volume disease?

To put these various therapeutic questions into perspective, currently the three most important therapeutic research questions are the following: definition of the role of the taxanes in front-line therapy, evaluation of high-dose approaches, and assessment of the roles of doxorubicin and hexamethylmelamine in front-line treatment.

A somewhat delicate but important concern is the identification of those institutional capabilities necessary for optimal management of the patient with ovarian carcinoma. Although there was not uniform agreement, a majority felt that it was important to design analyses of existent databases to determine whether specific capabilities (for example, specific types of surgical or chemotherapeutic expertise) were associated with better survival. It is recognized that such issues are difficult to study.

Finally, quality control issues were regarded as critically important in the conduct of clinical trials. Consensus recommendations are that, as a minimum, strict guidelines should be observed with regard to the details of surgical procedures to be performed, the review of all pathology material, and the determination of the dose and timing of chemotherapy.

Dose intensity

Implications for standard practice

Well designed clinical trials are vital to address numerous questions remaining with regard to the importance of dose intensity of standard agents and to the optimum integration of taxanes into the overall management of ovarian cancer patients.

General comments made by the group regarding standard chemotherapy regimens were:

- There is no evidence that cisplatin doses greater than 25 mg/m^2/wk in multiagent regimens or 30 mg/m^2/wk as a single agent are useful.
- There is no evidence that using cytokines in the presence of neutropenia is necessary and superior to decreasing drug doses in the face of severe myelosuppression.
- There is no conclusive evidence that high dose therapy with autologous bone marrow transplantation or peripheral blood stem cell support is beneficial in any subset of patients with epithelial ovarian cancer.
- Though most patients with advanced ovarian cancer who achieve a clinical complete remission will ultimately relapse, there is no firm evidence that prolonged treatment with any agent or modality prevents or delays recurrences.
- Intraperitoneal chemotherapy is based on the concept that the intra-abdominal administration of drugs can produce high concentrations locally and give adequate systemic levels as well. Despite the initial enthusiasm among researchers, the benefits of intraperitoneal chemotherapy could not be established. So far there is no place for intraperitoneal treatment outside the research setting.

Research issues

- High dose chemotherapy approaches which require cytokines, autologous bone marrow support and/or peripheral blood stem cell transfusions should focus on patients with drug sensitive small volume disease. Randomized trials of high dose therapy should be performed. Carboplatin should be the platinum compound which is studied at high dose.
- High dose carboplatin and paclitaxel combinations need to be examined in feasibility studies and compared to a 'standard' carboplatin (AUC of 5–7) plus paclitaxel (135–175 mg/m^2) combination.
- Late intensification with high dose chemotherapy and peripheral blood stem cell transfusions should be compared to standard doses of the same drugs in patients who achieve a pathologically confirmed complete remission or who have microscopic residual disease.

Supportive care

Implications for standard care

At present there is no evidence that commercially available cytokines are routinely necessary to maintain dose intense regimens in patients with advanced disease. No cytokine has yet been demonstrated to be clinically useful in protecting against thrombocytopenia.

There is no evidence that any form of 'neuroprotective' agent is clinically useful.

Research initiatives

Clinical trials of new cytokines with the potential to reserve thrombocytopenia (IL-1d, IL-11, IL-3, PIXY 321) are necessary.

Research initiatives to develop agents capable of decreasing neurotoxicity of platinum compounds and taxanes await the demonstration that dose intensity and cumulative dose are critical factors for increasing survival.

Drug resistance

Implications for standard practice

There is no evidence that any modulator of drug resistance is of benefit in refractory ovarian cancer patients.

Implications for research

The establishment of ovarian cancer tumour banks is critical to provide tumour specimens to basic investigators studying clinical drug resistance.

Among mechanisms of resistance which need further study in ovarian cancer are: efflux pumps (MDR) and other transport proteins, intracellular drug inactivation either by enzymatic deoxification (flutathione transferases) or by binding to thiol rich proteins (metallothionein) or to glutathione, repair of cytotoxic adducts to DNA, alterations in tubulin structure, and novel mechanisms such as the role of signal transduction pathways and growth factors in drug resistance.

Agents such as buthionine sulfoximine which have been shown to reverse drug resistance in relevant model systems of ovarian cancer are ready to clinical evaluations.

Second-line treatment

In general, patients receiving second-line treatment are not curable at present, thus the toxic effects of treatment must be balanced against the probable benefit of any intervention. Treatment should be considered when patients have disease-related symptoms. The reinstitution of treatment on the basis of a CA 125 evaluation alone or in the case of a non-resectable, asymptomatic recurrence is controversial. It should be noted that some studies suggest that the chance of response to second-line therapy is higher when the volume of recurrent disease is small. Recommendations can be made for the three categories of patients.

1. Progression in patients who have not received platinum. If patients have not received platinum, a platinum-containing regimen is indicated.

2. Progression on platinum. If patients are resistant to platinum (progression during platinum) the probability of a benefit from a second platinum compound is so low that it is not recommended. Furthermore, therapy with any of the agents currently available (anthracyclines, taxanes etc.) is of limited value in this group of patients. Enrolment of such patients on phase II trials of investigational approaches is encouraged.

3. Progression after platinum. Patients who relapse after completing their first-line platinum therapy will respond again to platinum compounds with the probability of response being highly increased by the increasing length of the intertreatment interval. Other agents shown to be of value in this setting include taxanes. Although both agents have shown activity in this group of patients, toxic effects are different and this may be relevant in treatment selection.

Role of surgery. The role of surgery is being reevaluated in relapsed disease. Selected patients with long disease-free interval and resectable (e.g. solitary) lesion may be considered for surgical resection.

Investigational drugs

Investigational new drugs testing can be considered in the following three groups of patients.

1. Patients who are progressing during the use of platinum compounds. Clinical trials in these patients help to identify new agents active in platinum refractory disease. Eligible patients include those with measurable disease, WHO performance states 0, 1, 2, and more than 4 weeks since last therapy. A study endpoints objective tumour regression (preferably documented by imaging evaluation and ideally confirmed by third party review) is advocated. In trials enroling this group of patients the sample size and stopping rules should be written to detect a true response rate of more than 15% (no response in 20 patients, the trial closes).

2. Patients relapsing after a treatment free interval since last platinum administration. Even though some patients in this category may achieve a second response to platinum or to other agents (e.g. taxanes), a trial of investigational therapy can be justified prior to retreatment since these patients are not curable. Eligibility and endpoints can be similar as under 1, but sample size and stopping rules should be defined to detect a

true response rate of more than 20% (no response in 15 patients, the trial closes).

3. Previously untreated patients with unfavourable prognostic factors (e.g. FIGO stage IV patients). The use of investigational agents in this group of patients is controversial and should be performed with great caution. Some investigators feel that a case can be made for studying investigational drugs shown to be active in relapsed or refractory patients in the first-line setting to identify the single agent response rate in a more favourable population. If this is done, care must be taken to insure that patients are selected appropriately (non-curable disease, no immediately life-threatening complications). Exclusions might include imminent or actual bowel obstruction. This is so that very ill patients are not denied the potential palliative benefit of retreatment with platinum. The design must include early cross-over to conventional therapy if tumour regression is not seen after a limited number of cycles. In this group of patients the sample size and stopping rules should be written to detect a true response of more than 40% (no response in 8 patients, the trial closes).

In all studies using investigational drugs in ovarian cancer the reports must include the following: all previous treatment (with or without cisplatin or taxanes), time since diagnosis, last treatment, time since last treatment, tumour size at start of the investigational drug, method of detecting relapse (with or without the use of CA 125), percent doses of treatment given, frequency of tests to evaluate toxicity, and definition of response.

Tumour markers

Clinical recommendations

CA 125 should not be routinely applied for the screening of ovarian cancer. In patients who are suspected of having ovarian cancer, CA 125 should be obtained in conjunction with other clinical evaluations, including sonography.

Serum CA 125 level should be obtained routinely prior to initial surgery and in patients with documented ovarian cancer just prior to the initiation of chemotherapy. The use of CA 125 as a prognostic indicator should not be applied to routine clinical practice.

During chemotherapy for ovarian cancer CA 125 should be performed routinely at regular intervals. Other appropriate clinical assessments, such as pelvic examination, radiography and sonography should be performed when clinically indicated. At present there is insufficient evidence for the use of CA 125 as the sole criterion for diagnosing progressive disease and making management decisions.

There is no consensus regarding the routine use of CA 125 for follow-up of ovarian cancer. Patient management should be carried out at the discretion of the individual practitioner, and the test when used, should be part of an overall evaluation of the patient. However, once there is any suspicion of relapse based on symptoms or signs of disease, CA 125 levels are recommended. Therapeutic intervention should not be based solely on the CA 125 result.

No other serum tumour markers should be applied routinely in the clinical setting at this time, as they do not have sufficient specificity or sensitivity to predict outcome, and in most cases do not give information complementary to the CA 125.

Research recommendations

With regard to screening for ovarian cancer, the CA 125 should be used in a study of potentially high risk women, such as those with two first degree relatives who have ovarian cancer.

The use of CA 125 as a prognostic indicator should be considered for use in stratification in clinical trials, preferably using absolute level criteria after 2 or 3 courses of therapy.

Finally CA 125 should be used to define new criteria for response and progression using serial CA 125 levels. The goal of the research should be to develop reliable criteria that could be applied to measure response and progression. Thes criteria could be used to modify existing WHO criteria.

References

1. Thigpen T, Bertelsen K, Eisenhauer EA et al. Long-term follow-up of patients with advanced ovarian carcinoma treated with chemotherapy. Ann Oncol 1993; 4 (Suppl. 4): S35–S40.
2. Ovarian Cancer Meta-Analysis Project. Cyclophosphamide plus cisplatin versus cyclophosphamide, doxorubicin, and cisplatin chemotherapy of ovarian carcinoma: A meta-analysis. J Clin Oncol 1991; 9: 1668–74.
3. Vermorken JB, ten Bokkel Huinink WW Eisenhauer EA et al. Carboplatin versus cisplatin. Ann Oncol 1993; 4 (Suppl. 4): S41–S48.
4. Calvert AH, Newell DR, Gumbrell LA et al. Carboplatin dosage: Prospective evaluation of a simple formula based on renal function. J Clin Oncol 1989; 17 (11): 1748–56.
5. McGuire WP, Hoskins W, Brady M et al. A phase II trial comparing cisplatin/cytoxan and cisplatin/taxol in advanced ovarian cancer. Proc Amer Soc Clin Oncol 1993; 12: 255.

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